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AUTHORS' REPLY

DR SHAPIRO raises an important methodologic issue, namely, the potential for selection bias associated with the use of "lifestyle" drugs among participants in a breast cancer screening program. His review of our studies, however, conveys the impression that all our results have been distinctly positive. This isn't so. In the analyses reported in this journal, the overall relative risk (RR) associated with thyroid supplements was 1.2 with "patterns of risk by duration and latency that failed to provide evidence of causality". Elsewhere [1], we have reported that the RR associated with use of oral contraceptives was 1.1 with "no indication of increasing risk with years of use or years since initial use". For menopausal estrogen use [2], we found an overall RR of 1.2 with no evidence of a duration–response for the total group. The multiplicity and consistency of findings in *a priori* designated subgroups, however, suggested a "possible, although complex, relationship between estrogen use and risk of breast cancer". We also evaluated use of diazepam (valium) and found no association overall [3], and no evidence that diazepam promotes or accelerates breast cancer growth [4], as suggested by some clinical and experimental observations. With the possible exception of menopausal estrogen use, all our results resemble those of Dr Shapiro and associates in their hospital-based case–control studies. One of the advantages of a large case–control study is the ability to evaluate risk in subgroups. While this has the potential for revealing important biologic insights into etiology, the results need to be interpreted cautiously and in the context of the overall findings.

Dr Shapiro's discussion of the results from a study of antihypertensive drug use [5] is difficult to address. As he notes, this was a study with which we were not associated and that was conducted by mail questionnaire, at the height of the reserpine controversy, and on a relatively small sample of women in the screening program. However, our own analyses of the home-interview data from a large series of subjects in the screening program provide no overall evidence of an elevated risk associated with the use of reserpine or other antihypertensive drugs [6].

Although our findings overall do not suggest a positive effect for medications related to "lifestyle" or recruitment to long-term medical care, Dr Shapiro seems to be using our publications to contend that the very opportunity for selection bias invalidates the use of screening programs to evaluate possible drug associations. However, as Dr Shapiro points out, the issue is not whether women preferentially using such drugs attend screening programs, but whether those who use these medications and develop breast cancer preferentially attend these programs compared to drug-using women without disease. He presents a scenario that he believes might lead to this bias.

Perhaps the most convincing argument against this bias is the similarity between our results for the prevalent and the incident cases. If a drug-using case is more likely to be in the program because she is symptomatic, then one would expect the effect to be present for cases diagnosed at the initial exam, and absent for those who joined the program at the same time but did not develop clinically detectable disease until a year or more later. This pattern was not seen for thyroid medications (RR = 1.3 for cases diagnosed at the first exam and 1.6 for those detected subsequently) or for any of the other drugs we have thus far evaluated. Dr Shapiro considers this point, but feels that an analysis which excludes the prevalent cases and is confined to the incident cases might still be subject to selection bias because of selective retention in the program (i.e. "those who first notice lumps between screening encounters will more commonly keep their next appointments than those who do not notice lumps"). However, our study did not include only those cancers identified at the annual screening exams. In fact, all women who were initially recruited for screening were followed

for the duration of the program and all cases (screening detected, interval cancers, and cancers in drop-outs) were included. Thus, the incident series is at least as unbiased as standard hospital or registry-based studies in including "virtually all cases", with the advantage that the population base has been identified, enumerated, and characterized.

The potential for selection bias may also be evaluated by a variety of other means. If an appreciable number of women lied about being asymptomatic when they were recruited to the program, one would expect to see a much smaller proportion of so-called "minimal" breast cancers (those too small to be detected by the woman herself) found at the first exam as opposed to later. In fact, minimal cancers accounted for 33% of the prevalent cancers and 32, 34, 31, and 30% of those detected at exams 2, 3, 4, and 5, respectively [7]. If selection bias were operating, one would also expect positive associations with "lifestyle" drug use for the larger breast cancers, and no associations for the minimal lesions. This has not been the case. Although not previously published, the RR's for oral contraceptive use among the larger invasive, small invasive and *in-situ* malignancies were 1.2, 1.0, and 1.0, respectively. The corresponding RR's for menopausal estrogen use were 1.0, 1.3, and 0.9. As already published, the findings for diazepam use revealed no increase in RR for the smallest lesions, and a progressively stronger "protective" effect with increasing size of tumor or stage of disease [4]. This pattern prompted our concern about an opposite kind of selection bias, that is, whether some prescription drug users might be more health conscious, and thus more likely to have breast abnormalities evaluated before entering a screening program. Thus, such individuals might have had palpable breast tumors already diagnosed, compared to non-drug using women with similar pathology. This type of bias would diminish the opportunity to identify true drug effects. Fortunately, the ability to compare the prevalent and incident series was useful in assessing and dismissing the likelihood of such a bias associated with diazepam use.

If the selection bias that concerns Dr Shapiro were operating, one would also expect it to apply equally to breast cancer and biopsy-negative (benign disease) patients. A woman coming to a screening program because of symptoms is unlikely to be able to distinguish breast cancer from non-malignant abnormalities that would justify biopsy. With the exception of a prior history of benign disease, virtually none of the breast cancer risk factors were associated with the development of benign breast disease in this screening program [8]. In addition, while no overall association between breast cancer and oral contraceptives was found, the expected level of protection (RR = 0.8) between these drugs and benign disease was observed. Also, while finding no duration–response relationship overall between menopausal estrogen use and breast cancer risk, a marked positive association, with histologic specificity, was noted for benign breast disease [9].

Finally, if an important selection bias were operating for "lifestyle" drugs one would expect to see a diathesis of increased risks associated with use of several drugs in this program. As we have explained, this has not been the case with oral contraceptives, diazepam or thyroid medications. Even for menopausal estrogens, the suggested relationship was a complex one that lacked characteristics usually seen with established risk factors.

In any investigation, it is important to assess the potential for various kinds of bias. In the breast screening program, we have extensively evaluated the opportunities for selection bias associated with drug use. No direct or indirect evidence for such a bias has been found. This has strengthened our belief that this study population will continue to be useful in the evaluation of breast cancer risk factors. Furthermore, we do not believe there is a "gold standard" with respect to the major type of epidemiologic investigation (e.g. cohort, case–control) or its many subtypes (e.g. population-based, hospital-based, mortality-based, record-review, home interview, mail interview, pre-paid health plans, screened populations, prevalent cases, incident cases). Rather, we view the strengths and weaknesses of many of these methods as distinctly complementary. Well-designed and executed studies of each type can contribute uniquely to important etiologic questions. When a variety of such studies conducted by different investigators reach the same overall conclusions, confidence in the results is substantially increased. Thus far, there has been substantial agreement about the breast cancer risks associated with commonly used medications such as oral contra-

ceptives, minor tranquilizers, menopausal estrogens and thyroid supplements. Some issues still remain to be resolved and will continue to require a variety of epidemiologic approaches.

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